PATENT

DOCKET NO: 17302(HL)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Forman et al

Serial No.: 09/590,447
Conf. No.: 1446
Filed: June 9, 2000

For: METHODS FOR MODULATING FXR RECEPTOR ACTIVITY

Examiner: Hui, S.

Group Art Unit: 1617

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Date of Signature: 6/30/2003

AMENDMENT

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

This communication is responsive to the Office Action received January 29, 2003. The Office Action has been carefully considered, and Applicants have the following comments.

Serial No. : 09/590,447
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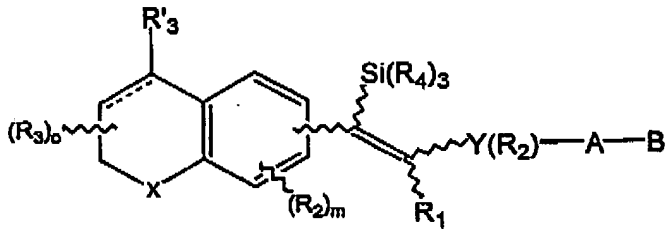
AMENDMENTS AND STATUS OF CLAIMS

1. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of administering to a mammal in need thereof a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said synthetic FXR ligand comprising a compound of the formula



formula (3)

wherein the dashed line represents a bond or absence of a bond;

X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or C_1 - C_{12} alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

[R_3] R'3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$-phenyl, $(R_{15})_r$-naphthyl, or $(R_{15})_r$- heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, $NH(R_8)$, COR_8, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH, NO_2, $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH, $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

2. (Original) A method in accordance with Claim 1 where X is (C(R1)2)n and n is 1.

3. (Original) A method in accordance with Claim 1 where X is S.

4. (Original) A method in accordance with Claim 1 where X is O.

5. (Original) A method in accordance with Claim 1 where X is NR.

6. (Original) A method in accordance with Claim 1 where Y is phenyl.

7. (Original) A method in accordance with Claim 1 where Y is thienyl.

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8. (Original) A method in accordance with Claim 1 wherein said compound has a structure selected from formulas (1) and (2).

9. (Original) A method in accordance with Claim 8 wherein said compound has a structure of formula (1) where the dashed line represents absence of a bond.

10. (Original) A method in accordance with Claim 8 wherein said compound has a structure of formula (1) where the dashed line represents a bond.

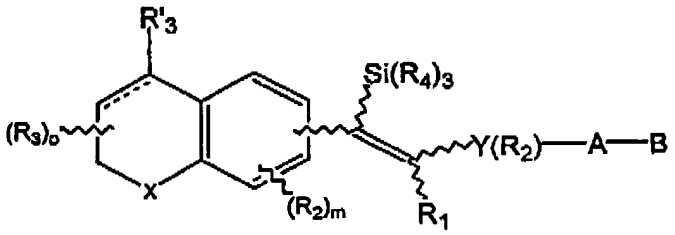
11. (Original) A method in accordance with Claim 1 wherein said compound has a structure selected from formulas (3) and (4).

12. (Original) A method in accordance with Claim 11 wherein said compound has a structure of formula (3) where the dashed line represents absence of a bond.

13. (Original) A method in accordance with Claim 11 wherein said compound has a structure of formula (3) where the dashed line represents a bond.

14-30 (Withdrawn)

31. (Previously amended) A method of treating a hypercholesterolemic mammal comprising the steps: administering to a mammal in need thereof a pharmaceutically acceptable composition comprising an FXR antagonist having the following formula



formula (3)

wherein the dashed line represents a bond or absence of a bond;

X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted

alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or C_1 - C_{12} .alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

R'_3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$-phenyl, $(R_{15})_r$-naphthyl, or $(R_{15})_r$- heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, $NH(R_8)$, COR_8, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH, NO_2, $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH, $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

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32. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of providing to said mammal a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor.

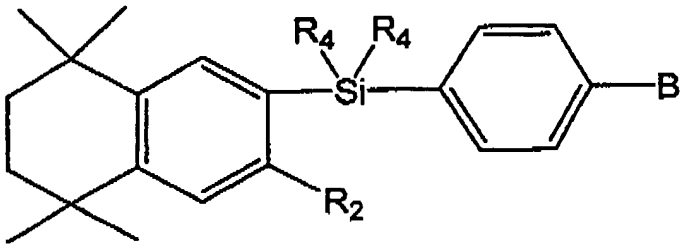
33. (Original) The method of claim 32 wherein said pathological condition comprises hypercholesterolemia.

34. (Original) The method of claim 32 wherein said pathological condition comprises hypocholesterolemia.

35. (Original) The method of claim 32 wherein said pathological condition is characterized by the overproduction of bile acids.

36. (Original) The method of claim 32 wherein said pathological condition is characterized by the underproduction of bile acids.

37. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of administering to a mammal in need thereof a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said synthetic FXR ligand having the formula



wherein R_2 is H or lower alkyl, R_4 is lower alkyl of 1 to 8 carbons and B is CH_2OH or $COOR_8$ where R_8 is H or ethyl.

38. (Original) A method in accordance with Claim 31 where R2 is H and R4 is ethyl.

39. (Original) A method in accordance with Claim 32 where B is CH2OH.

40. (Original) A method in accordance with Claim 33 where B is COOR8.

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REMARKS

Applicants that the Examiner for the helpful suggestions contained in the January 29, 2003 Office Action, and for indicating that the claims, amended as above, are allowable. The claim Amendments made herein render moot the rejections pursuant to 35 USC 112(1) and 35 USC 112(2)

Therefore the claims appear to be in condition for allowance. Please use Deposit Account 01-0885 for the payment of the extension fees or any other fees due in connection with the current response.

Respectfully submitted,

Dated: 6/30/03

By: _____
Carlos A. Fisher
Registration No. 36,510
Attorney of Record

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714-246-4920
Facsimile: 714-246-4249

COPY

MAIL STOP AMENDMENT - FEE

Rec'd in USPTO/PCT Office. Date Stamp and Return Card.
Date: 6/30/2003 Serial No.: 09/590,447; Conf. No 1446
Title: METHODS FOR MODULATING FXR RECEPTOR.
Dkt. No.: 17302 (HL)
Enclosed Are:

- _ Specification # ____, Claims # ____, and Abstract # ____
- _ Drawings (____ sheets)
  ____ Formal ____ Informal
- _ Info. Disc. Statement
- _ Priority Documents # ____
- _ PTO 1449 W/References
- _ PCT Request (# pgs. ____)
- _ PCT Demand (# pgs. ____)
- _ PCT Response (# pgs. ____)
- _ PCT Amendment (# pgs. ____)
- _ Declaration, Power of Attorney
- _ Assignment & Cover Sheet
- ✓ Amendment ~~(Final)~~ (# pgs. 7)
- ✓ Certificate of Mailing
- _ Issue Fee Transmittal
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- ✓ Extension of Time - 2 months
- _ Express Mail No. _____
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- _ _____
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- _ _____
- _ _____

TO: Sam Hui

ALLERGAN
LEGAL DEPARTMENT
2525 Dupont Drive
Irvine, California 92612

Fax No. 703-746-3123

FROM: CARLOS A. FISHER
Telephone-714-246-4920
FAX NO.: 714-246-4249

DATE: October 28, 2003

Pages being sent including this cover page:

cc:

Re: Privacy Gap Analysis

This fax has been sent to one number only- please copy ALL OTHER addressees in your location/country.

____x__ ORIGINAL WILL NOT FOLLOW

____ORIGINAL WILL FOLLOW VIA:
_____ Regular Mail
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Attached is a copy of the Response as filed on July 31, 2003.

UNITED STATES PATENT AND TRADEMARK OFFICE
UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, DC 20231
www.uspto.gov

Paper No.

Notice of Non-Compliant Amendment (Voluntary Revised Practice)

The amendment filed ___July 2, 2003_____ under the voluntary revised amendment practice guidelines[1], published in the Official Gazette on February 25, 2003 (*Amendments in a Revised Format Now Permitted,* 1267 Off. Gazette 106), does not fully comply with minimal requirements of the voluntary practice. In order for the amendment to be entered, it must either (1) comply with the guidelines of the voluntary revised amendment practice (which practice invokes waivers of certain 37 CFR 1.121(a)-(d) requirements) or (2) comply with current 37 CFR 1.121 requirements.

THE FOLLOWING ITEM(S) IN APPLICANT'S AMENDMENT CAUSES THE AMENDMENT TO BE NON-COMPLIANT WITH THE VOLUNTARY REVISED AMENDMENT PRACTICE.

☐ 1. A complete listing of all of the claims is not present in the amendment paper.

☐ 2. The listing of claims does not include the text of all claims currently under examination.

☐ 3. The claims of this amendment paper have not been presented in ascending numerical order.

☒ 4. Each claim has not been provided with a status identifier, and, as such, the individual status of each claim cannot be determined.

☒ 5. Other: Claims 14-30 have the wrong status identifier

LIE: Check one of the following boxes:

☐ **PRELIMINARY AMENDMENT:** Applicant is given ONE MONTH from the mail date of this letter to re-submit the amendment in compliance with either the guidelines of the revised amendment practice or current 37 CFR 1.121. Failure to comply with either the current 37 CFR 1.121 practice or with the voluntary practice will result in non-entry of the amendment and examination on the merits will commence without entry of the originally proposed preliminary amendment. This notice is not an action under 35 U.S.C. 132, and this ONE MONTH time limit is not extendable.

☒ **AMENDMENT AFTER NON-FINAL ACTION:** Since the above-mentioned reply appears to be a *bona fide* response, applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit an amendment which complies with either the voluntary practice guidelines or current 37 CFR 1.121 in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).

Brenda Brooy
Team Leader

[1] For further explanation of the guidelines of the revised amendment format, please see the posted notice and sample amendment format at:
http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf and
http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/formatrevamdtprac.pdf

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- _ Issue Fee Transmittal
- _ Transmittal Letter
- _ Extension of Time
- _ Express Mail No. ____
- ✓ Copy of 6/30/03 Amend.
- ✓ Corrected Claims
- ✓ NON-COMPLIANCE NOTICE

MAIL STOP -REPLY -NON-COMPLIANCE

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